In Utero through Lactational Assay Questions for EDMVS

Detailed Review Papers have been prepared to review the scientific principles underlaying an assay thus setting forth its theoretical relevance to the assessing the issue or endpoints of concern, review the methods that have been used for measuring the endpoints of concern, identify a protocol or data gaps that must be addressed to determine a protocol suitable for use in the EDSP, and finally recommend what studies should be conducted during the pre-validation phase to address the data gaps and demonstrate the relevance of the protocol.

The In Utero-lactational DRP is a draft being given to you primarily to assist EPA in beginning pre-validation studies on the in uterolactational assay. However, we recognize that it is the first draft DRP being submitted to the Committee. EPA and the Contractor are still learning how to best display this information. Therefore, in addition to questions about study design, we are raising some questions regarding the format, degree of detail, etc of the document itself.

Please keep the following questions in mind as you review the document.

1) Was the DRP for the in utero through lactational assay effective in presenting the background information? Do you have any suggestions for improvement?

2) Have any important studies or protocols been over-looked?

3) Three protocols are examined as relevant to a relatively short term in uterolactational exposure assay. Do you have any comments on the recommended protocol in the DRP? (Do you think a quarantine period should be added? Do you agree with the route of administration and the start and end times for the gavage dosing? The postwean holding period? Are the days and numbers of animals selected for necropsy appropriate?)

4) There are up to 20 endpoints being measured in this assay. EPA believes it is appropriate to look at a broad range of endpoints in the pre-validation phase to determine which are most sensitive and efficient for inclusion in the optimized protocol for validation. Are the endpoints selected appropriate for inclusion at the pre-validation stage? Should any endpoints be added or removed?

5) The DRP recommended that the protocol be demonstrated in 1-3 chemicals? As a broad apical assay , the in uterolactational assay should be able to detect E, A and T effects through a broad range of mechanisms. How many chemicals do you believe are appropriate to demonstrate the relevance of the protocol at this initial stage of the pre-validation process? Do you have any recommendations for the chemicals (and suggested doses) that should be tested for the pre-validation? Please list in order of priority and provide reasons for your choices.

6) EPA believes that the pre-validation studies for the in uterolactational assay should be run at three dose levels plus a vehicle control. As a screen the assay could be run at only two doses in accordance with the guidance of the SAP/SAB. Do you agree with the recommendation to conduct the pre-validation studies at three dose levels plus a vehicle control?

7) The DRP did not provide a specific recommendation regarding the number of litters to be employed in the study. What do you believe to be the appropriate number of litters per dose level for the pre-validation studies?

8) EPA would like general agreement from the Committee with the Agencies approach for conducting the validation program for the in uterolactational assay. Generally, EPA believes that it is more efficient to include the widest range of chemicals in the pre-validation phase, after the relevance of the protocol has been demonstrated and optimized. However, due to time pressures of the settlement agreement, EPA is proposing to conduct the "chemical array study" in the lead laboratory in parallel with the multiple laboratory validation studies. Does the Committee agree with this approach?